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(21) International Application Number: PCT/DK99/00641 (22) International Filing Date: 19 November 1999 (19.11.99) (30) Priority Data: PA 1998 01534 20 November 1998 (20.11.98) DK (71) Applicant (for all designated States except US): COLOPLAST A/S [DK/DK]; Høltedam 1, DK-3050 Humlebaek (DK). (72) Inventor; and (75) Inventor/Applicant (for US only): MADSEN, Niels, Joergen [DK/DK]; Forelvej 18, DK-3450 Allerød (DK). (74) Common Representative: COLOPLAST A/S; Nilausen, Kim, Patent Dept., Høltedam 1, DK-3050 Humlebaek (DK).		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limits for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: A METHOD FOR STERILISING A MEDICAL DEVICE HAVING A HYDROPHILIC COATING (57) Abstract <p>A method for sterilising a medical device comprising a hydrophilic coating using radiation said method comprising the steps of bringing the medical device having such coating in contact with an aqueous liquid for wetting the hydrophilic coating, said liquid comprising a solution of a hydrophilic polymer and sterilising the device by applying a sufficient amount of radiation provides coated devices showing a significantly increased and prolonged water retention and lower friction coefficient when wet.</p>		

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Title

A method for sterilising a medical device having a hydrophilic coating .

Field of the Invention

The present invention relates generally to sterilisation of medical devices having
5 hydrophilic coatings and more specific to sterilisation using radiation. Further-
more, the invention relates to a sterilised set comprising a medical device
provided with a hydrophilic coating and a liquid for wetting the hydrophilic
coating, a method for protecting the hydrophilic coating of a medical device
having such coating during sterilisation using radiation as well as a medical
10 device having a hydrophilic coating said medical device showing, after sterilisa-
tion using radiation, a prolonged water drain off time and reduced friction force.

Description of the Related Art

It is known to coat medical devices, e.g. catheters for introduction into human
cavities such as blood vessels, digestive organs and the urinary system, with a
15 hydrophilic coating, normally as a minimum applied on that part of the surface
which is introduced or comes into contact with mucous membranes, etc., during
introduction of the device. Whereas such coating is not particularly smooth when
dry, so that the handling of the device may become inconvenient, it becomes
extremely slippery when it is swelled with water, preferably immediately before
20 introduction into the human body and thus ensures a substantially painless intro-
duction with a minimum of damage on tissue.

US patent No. 3,967,728 to Gordon discloses the use of a sterile lubricant for
deposition on and lubricating an uncoated catheter before use.

WO 86/06284 (Astra Meditech Aktiebolag) discloses a wetting and storing device
25 for a coated catheter in which the coating may be wetted using water or water
comprising common salt and possibly bactericidal compounds or other additives.

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GB patent application No. 2 284 764 (MMG (Europe Ltd)) discloses the application of a lubricious substance such as a water based jelly to the tip of a non-coated catheter prior to insertion into the urethra.

US patent No. 3,648,704 (Jackson) discloses a disposable catheter apparatus in
5 which a lubricant may be applied to the tip of the catheter prior to catheterisation.

A large number of methods are known for the production of hydrophilic surface coatings for improving the slipperiness of a catheter or other medical device.

These methods are most often based on the fact that the substrate to be provided with a hydrophilic surface coating, in the course of one or more process
10 stages with intermediary drying and curing, is coated with one or more (mostly two) layers, which are brought to react with one another in various ways, e.g. by polymerisation initiated by irradiation, by UV light, by graft polymerisation, by the formation of interpolymeric network structures, or by direct chemical reaction. Known hydrophilic coatings and processes for the application thereof are e.g.
15 disclosed in Danish Patent No. 159,018, published European Patent Application Nos. EP 0 389 632, EP 0 379 156, and EP 0 454 293, European Patent No. EP 0 093 093 B2, British Patent No. 1,600,963, US Patent Nos. 4,119,094, 4,373,009, 4,792,914, 5,041,100 and 5,120,816, and into PCT Publication Nos. WO 90/05162 and WO 91/19756.

20 According to a method disclosed in US Patent No. 5,001,009, a hydrophilic surface coating is prepared on a substrate by applying, in two stages or in one combined stage, on the substrate a primer reactive with or adhesive to the substrate and then the actual hydrophilic surface layer which, in this case, comprises polyvinylpyrrolidone [PVP] as the active constituent. By this method,
25 no chemical reaction takes place between the components of the two layers applied. When the product remains inside the body only for a short period, there may be a risk that water will be extracted from the hydrophilic surface coating and into the tissues of the surrounding mucous membranes etc., owing to a higher osmotic potential of said tissues. At the same time, there is a risk of
30 abrasion of the coating during insertion. As a result of the extraction of water or

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loss of coating, the hydrophilic surface coating will have a tendency to become less slippery and to stick to surrounding tissues, and the removal of the medical device from the body may cause pain or damage the tissue. This is especially a problem when carrying out urodynamic examinations via a catheter.

- 5 European Patent No. EP 0 217 771 describes a method of forming a hydrophilic coating in order to retain the slipperiness in use for a longer period of time by applying a non-reactive hydrophilic polymer surface layer to a substrate, applying to the non-reactive hydrophilic surface polymer a solution comprising a solvent and above 2% (weight per volume) of an osmolality-increasing compound
- 10 selected from the group consisting of mono and disaccharides, sugar alcohols, and non-toxic organic and inorganic salts, with the proviso that the osmolality-increasing compound is not a trihalogenide such as KI_3 (KI/I_2), and evaporating the solvent. EP 0 217 771 discloses that when wetting the catheters after drying, catheters having a coating of a non-toxic, osmolality increasing compound retain-
- 15 ing their slipperiness for longer times than corresponding untreated surfaces i.e. coated catheters dry more slowly. However EP 0 217 771 is silent with respect to storing the coated catheters in a wetted form or sterilisation or problems in connection herewith.

- International patent publication No. WO 94/16747 discloses a hydrophilic coating
- 20 with improved retention of water on a surface, especially a surface of a medical device such as a urethra catheter, prepared by applying to the surface in one or more process steps at least one solution of components that will combine to form the hydrophilic coating. During the final step, the surface is coated with an osmolality promoting agent which is dissolved or emulgated in the solution or in
- 25 the last solution to be applied when forming the hydrophilic coating. WO 94/16747 does not disclose cross-linked coatings.

- WO 89/09246 discloses solid shaped structures having a surface coated with crosslinked hydrophilic polymer, the coating being durable and exhibiting a low coefficient of friction when wet. It is stated that the degree of crosslinking is criti-
- 30 cal and is to be controlled by the operating conditions chosen as too much crosslinking reduces or completely eliminates the low friction surface property,

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and too little crosslinking negatively affects the durability of the coating. WO 89/09246 does not disclose the presence of a water soluble or osmolality-increasing compound in the coating.

All said coatings are developed for instant swelling immediately before use of the
5 medical device on which the coatings are applied.

It has been found, however, that most hydrophilic coatings lose their water retention and that the coefficient of friction increase when the coatings are stored in water for an extended period of time and/or particularly after sterilisation using irradiation or autoclaving.

10 Thus, there is still a need for a hydrophilic coating retaining water retention and low coefficient of friction when the coatings are stored in water for an extended period of time and/or particularly after sterilisation using irradiation or autoclaving.

Summary of the Invention

15 The present invention relates to a method for sterilising a medical device comprising a hydrophilic coating using radiation.

Furthermore, the invention relates to a sterilised set comprising a medical device provided with a hydrophilic coating and an aqueous liquid for wetting the hydrophilic coating.

20 Still further, the invention relates to a method of protecting the hydrophilic coating of a medical device having such coating during sterilising using radiation.

The invention further relates to a medical device comprising a hydrophilic coating said medical device showing, after sterilisation using radiation, a prolonged water drain off time and a reduced friction force.

25 The invention yet further relates to methods for preparing sterilised catheters having hydrophilic coatings.

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Detailed Description of the Invention

The present invention relates to a method for sterilising a medical device comprising a hydrophilic coating using radiation said method comprising the steps of bringing the medical device having such coating in contact with an aqueous liquid for wetting the hydrophilic coating, said liquid comprising a solution of a hydrophilic polymer and sterilising the device by applying a sufficient amount of radiation.

It has surprisingly been found that the water retention can be increased dramatically and the coefficient of friction can be kept low by adding hydrophilic polymers for example polyvinylpyrrolidone or copolymers containing N-vinylpyrrolidone, poly(meth)acrylic acid or copolymers containing (meth)acrylic acid or (meth)acrylic acid esters, polyacrylamides, polyvinylalcohol and copolymers of partially saponified vinylacetate copolymers, polyethyleneglycol, polyvinylmethylether, polyvinylmethylether-maleic anhydride and copolymers containing maleic-anhydride or maleic-acidesters or copolymers containing vinylmethylether, or copolymers thereof, or water soluble polysaccharides or derivatives thereof such as carboxymethylcellulose (CMC) or hydroxyethylcellulose or Xanthane or a derivative thereof to the liquid for wetting a hydrophilic coating and that these compounds also protect these properties during exposure to sterilisation using radiation when wetted with such wetting liquid.

Suitable hydrophilic polymers for the wetting agent may be mixtures of the preferred species stated above.

Without limiting the invention to any specific hypothesis, it is assumed that the effect may be ascribed to one or more of following effects:

1. Dissolved hydrophilic polymer chains in the aqueous liquid penetrate physically bound or crosslinked coatings and stabilise them. The thickness of the coating is increased which contributes to a higher capacity of retaining water.

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2. Dissolved hydrophilic polymer chains in the aqueous liquid penetrates physically bound or crosslinked coatings and prevent further crosslinking during irradiation.

3. Dissolved polymers may be chemically bonded to the hydrophilic coating
5 during irradiation in the aqueous liquid. This gives rise to a thicker layer of coating contributing to a higher capacity of retaining water.

It is preferred that the hydrophilic polymer is a synthetic polymer and especially that the hydrophilic polymer is at least compatible with and preferably of the same type as the hydrophilic polymer of the coating.

10 Also preferred are polysaccharides selected from the group consisting of cellulose derivatives and xanthans. Although polysaccharides show a tendency of break down on sterilisation using radiation, these compounds have still proven effective in giving a long retention time, a low friction. Normally such compounds show a very pronounced thickening effect in water and are used in relatively low
15 amounts.

In a preferred embodiment of the invention the cellulose derivative is CMC or a derivative thereof. CMC is suitably used in an amount from 0.005 to 3.0 %, depending on the molecular weight and degree of substitution of the polymer preferably about 0.5% giving very good results. When using xanthan, the amount
20 used is normally in the range from 0.005 to 1%, preferably about 0.15%.

In an especially preferred embodiment of the invention the hydrophilic polymer is a polyvinyl pyrrolidone (PVP).

The amount of polyvinyl pyrrolidone to be used according to the invention may vary and depends i.a. on the molecular weight of the specific PVP. The higher
25 the molecular weight, the higher is the tendency of gelling. Thus, the use of higher amounts of low molecular weight PVP gives an effect similar to the use of lower amounts of a higher molecular weight PVP. The amount of a PVP of a given molecular weight PVP to be used is easily determined by the skilled in the

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art by routine experiments testing the water retention. When using a PVP having a relatively low molecular weight above 1000 and preferably above 5000, an amount of 6% by weight has proven to be suitable giving a long retention time, a low friction and no problems with gelling.

- 5 It is also considered an aspect of the invention, when working with medical devices having physically bound or cross-linked hydrophilic coatings, to include a hydrophilic polymer not forming cross-links with the coating into the coating and to wet or store the medical device in water or saline.

- Saline or another non-toxic osmolality increasing agent is preferably present in
10 the physiological range. Thus, saline is preferably present in an amount of 0.9%

- Furthermore, the invention relates to a sterilised set comprising a medical device provided with a hydrophilic coating and an aqueous liquid for wetting the hydrophilic coating wherein said device is in contact with the aqueous liquid, wherein said set has been sterilised using radiation while in contact with said liquid
15 comprising a solution of a hydrophilic polymer.

In another embodiment of the set of the invention the aqueous liquid is placed in the package also comprising the medical device provided with a hydrophilic coating. Thus, the catheter is permanently wetted by the wetting liquid and thus ready to use. Such a set may be of the kind disclosed in WO 98/19729.

- 20 It has surprisingly been found that using wetting liquids of the kind disclosed above, it is possible to provide a catheter which is permanently wetted by the wetting liquid and thus ready to use and which may be sterilised by irradiation or autoclaving and which will retain the water retention capability and thus low coefficient of friction when the coatings are stored in water for an extended
25 period of time.

Sterilisation using radiation is normally carried out using beta or gamma radiation.

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Normally, a loss of water retention capability of coated catheters is observed, probably due to loss of non-crosslinked and non-bonded polymer chains from the coating during storage in water or by further crosslinking of the coating during irradiation in water.

- 5 In the first case a collapse of the coating, when the device is removed from the water reservoir, will give a low water retention and increase of the coefficient of friction during use. In the second case further crosslinking will decrease the water content in the coating and hence, the coating will show a low water retention and an increased friction coefficient.
- 10 Still further, the invention relates in a third aspect to a method of protecting the hydrophilic coating of a medical device having such coating during sterilising using radiation, characterised in that the coating is brought into contact with an aqueous solution comprising a hydrophilic polymer and exposed for the radiation while in contact with the aqueous solution.
- 15 In a fourth aspect, the invention relates to a medical device comprising a hydrophilic coating said medical device showing, after sterilisation using radiation, a water drain off time > 3 minutes and a friction force of < 0.05 N when testing a 10 cm tube having the hydrophilic coating fixed on a stainless steel plate with two stainless steel rods as shown in ASTM 1894-93 for both physically bonded
- 20 hydrophilic coatings of the type disclosed in WO 94/16747 and for chemically cross-linked coatings of the types disclosed in i.a. WO 98/58988, WO 98/58989, and WO 98/58990.

Using the invention it has proven possible to obtain and retain very high water drain off time and low friction forces.

- 25 In a fifth aspect, the invention relates to a method of preparing a sterilised catheter having a crosslinked two-layer hydrophilic coating comprising the steps of
 - a) preparing a solution of polyvinyl pyrrolidone dissolved in an ethanol/gamma butyrolactone solvent mixture,
 - b) dipping a raw catheter in the solution and letting it dry at ambient temperature,

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- c) dipping the resulting catheter in a PVP-solution containing urea and an ethanol/gamma butyrolactone (85/15) solvent mixture,
- d) further drying at elevated temperature,
- e) cross-linking the polyvinylpyrrolidone by exposing the coated catheter to
- 5 UV-light having a wave length range between 200 and 300 nm. for from ½ to 15 minutes, and
- f) sterilising the coated catheter while wetted with a. solution of PVP by irradiation.

- In a sixth aspect, the invention relates to a method of preparing a sterilised
- 10 catheter having a crosslinked hydrophilic coating with unsaturated Poly(methyl vinyl ether/maleic anhydride)/hydroxyethylmethacrylate(HEMA) prepolymers comprising the steps of
 - a) preparing a solution of poly(methyl vinyl ether/maleic anhydride) in acetone in a reaction vessel equipped with at stirrer, keeping the reaction mixture at room
 - 15 temperature while adding 1-methylimidazole as a catalyst and hydroxyethyl-methacrylate dropwise to the stirred polymer solution during a period of 30 minutes,
 - b) stirring the mixture for from few minutes to 10 hours at room temperature,
 - c) preparing a primer mixture by dissolving a medical grade polyurethane and the
 - 20 poly(methyl vinyl ether/maleic anhydride)/HEMA unsaturated prepolymer in a mixture of THF and acetone,
 - d) coating a raw catheter with a primer by dipping in the resulting solution in a manner known per se,
 - e) dipping the resulting catheter in the solution of poly(methyl vinyl ether/maleic
 - 25 anhydride)/HEMA unsaturated prepolymer in acetone for applying a top coat,
 - f) drying the resulting catheter,
 - g) cross-linking the poly(methyl vinyl ether/maleic anhydride)/HEMA unsaturated prepolymerpolyvinylpyrrolidone by exposing the coated catheter to 5 M rads from a high energy electron beam source, and
 - 30 h) sterilising the coated catheter while wetted with a. solution of PVP by irradiation.

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In a seventh aspect, the invention relates to a method of preparing a sterilised catheter having a cross-linked single layer of hydrophilic coating comprising the steps of

- a) preparing a solution of polyvinyl pyrrolidone dissolved in an ethanol/gamma
- 5 butyrolactone solvent mixture,
- b) dipping a raw catheter in the solution and letting it dry at elevated temperature,
- c) cross-linking the polyvinylpyrrolidone by exposing the coated catheter to UV-light having a wave length range between 200 and 300 nm. for from ½ to 15 minutes, and
- 10 d) sterilising the coated catheter while wetted with a. solution of PVP by irradiation.

In accordance preferred embodiment of the invention the wetting liquid comprise an antibacterial agent such as a silver salt, e.g. silver sulphadiazine, an acceptable iodine source such as povidone iodine (also called polyvinylpyrrolidone

15 iodine), chlorhexidine salts such as the gluconate, acetate, hydrochloride or the like salts or quaternary antibacterial agents such as benzalkonium chloride or other antiseptics or antibiotics. Antibacterial agents reduces the risk of infection, especially when performing urodynamic examinations.

The wetting liquid may according to the invention comprise an osmolality

20 increasing agent such as urea, sodium chloride and/or any salt or organic low molecular weight compound being physiological acceptable and non-irritating for adjusting the ion strength of the coating approximately to the physiological range, the coating preferably being isotonic in use.

When using urea, the added amount may vary within very broad limits.

- 25 The wetting liquid of the invention may also, if desired, comprise plasticizers for the hydrophilic coating such as diethylene glycol, glycerol, phthalates, sorbitol or the like.

Indicators or buffers for pH or antibodies, e.g. monoclonal antibodies for specific proteins, may also be enclosed in the wetting liquid of the invention.

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In accordance with a preferred embodiment pharmaceutically active compounds such as antioxidants or preservatives such as anti microbial agents or antithrombogenic agents may be added to the composition.

Materials and Methods

- 5 Polyvinylpyrrolidone: PVP K 90 available from ISP Inc. having a molecular weight 1,300,000 according to ISP.

Polyvinylpyrrolidone: Plasdone K-25 available from ISP Inc. having a molecular weight 34,000 according to ISP.

- 10 Poly(methyl vinyl ether/maleic anhydride) is available as the Gantrez AN series of copolymers from ISP

Ethanol: Absolute Alcohol.

Gamma butyrolactone: Gamma-butyrolactone from International Speciality Products.

UV catalyst: ESACURE KIP 150 from Lamberti SpA

- 15 Darocure® 1173 from Ciba Geigy.

Method for Determination of the Friction.

The Standard Test Method for Static and Kinetic Coefficient of Friction of Plastic Film and Sheeting, ASTM D 1894 - 93 was modified for testing the friction coefficient and wear on plastic tubes and catheters.

- 20 The tubes or catheters were cut in lengths of 10 cm and fixed on a stainless steel plate with two stainless steel rods as shown in ASTM D 1894 - 93. The rods had diameters comparable with the inner diameter of the tubes or catheters to keep their shape even when heavy sledges were placed upon them.

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The friction was determined after wetting after dipping the specimen in wetting liquid for 1 minute. The force for pulling the sledge was measured in Newtons.

Method for Determination of Water Retention

Water retention was determined by subjectively determining the time for the liquid to drain off after which the coating is dry using a stop watch.

Experimental Part

Example a.

Preparation of a catheter having a crosslinked two-layer hydrophilic coating.

5 parts of PVP K 90 and 0,05 parts of ESACURE KIP 150 were dissolved in 94,95 parts of an ethanol/gamma butyrolactone solvent mixture. PVC-catheters were dipped in the solution and dried 1 minute at ambient temperature and then dipped in a PVP-solution containing 5 parts of PVP, 1 part of urea and 94 parts of an ethanol/gamma butyrolactone (85/15) solvent mixture. The catheters were further dried for 30 minutes at 70°C and exposed to UV-light having a wave length range between 200 and 300 nm. for 5 minutes.

Finally, sterilisation of the coated catheter was performed while wetted with a solution of PVP using irradiation.

Example b.

Preparation of a catheter having a crosslinked hydrophilic coating with unsaturated Poly(methyl vinyl ether/maleic anhydride)/hydroxyethylmethacrylate(HEMA) prepolymers.

20 parts of Gantrez® AN 119 was dissolved in 200 parts of acetone in a reaction vessel equipped with a stirrer. The reaction mixture was kept at room temperature. One drop of 1-methylimidazole was added to the solution as a catalyst. 5 mole % 2-hydroxyethylmethacrylate, based on contents of maleic anhydride were added dropwise to the stirred polymer solution during a period of 30 min. The mixture was stirred for further 2 hours at room temperature.

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A 50:50 primer mixture with 5% solids was prepared by dissolving a medical grade polyurethane and the Poly(methyl vinyl ether/maleic anhydride)/HEMA unsaturated prepolymer in a 50:50 mixture of THF and acetone and was coated on PVC catheters as a primer by dipping in a manner known per se.

- 5 The catheters were dipped in the solution of poly(methyl vinyl ether/maleic anhydride)/HEMA unsaturated prepolymer in acetone for applying a top coat, dried and exposed to 5 M rads from a high energy electron beam source.

Afterwards, the cross-linked coatings were hydrolysed and neutralised in a sodium hydrogen carbonate buffer solution for one hour before drying.

- 10 Then, sterilisation of the coated catheter was carried out while wetted with a solution of PVP using irradiation.

The friction tested according to the modified ASTM D 1894 - 93 method as described above showed a friction force of 0.02 when determined in water.

Example c

- 15 A top coat and a primer solution were prepared as in Example b. To the solutions was added 1% by weight of the solid Darocure® 1173, a UV photo-initiator obtainable from Ciba Geigy.

- PVC catheters were dipped in the primer solution, dried for 30 minutes and dipped in the top coat solution also containing 1% by weight of the solid of
20 Darocure® 1173 and dried for further 30 minutes. Then, the coating was cross-linked by exposure to UV light.

The cross-linked coatings were then hydrolysed and neutralised in a sodium hydrogen carbonate buffer solution for one hour before drying.

- The sterilisation of the coated catheter was carried out while wetted with a.
25 solution of PVP using irradiation.

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The friction tested according to the modified ASTM D 1894 - 93 method as described above showed a friction force of 0.02 when determined in water.

Example d

Preparation of a catheter having a cross-linked single layer hydrophilic coating

5 according to the invention.

5 parts of PVP K 90 was dissolved in 95 parts of a ethanol/gamma butyrolactone (85/15) solvent mixture. PVC catheters were dipped in the solution, dried for 30 minutes at 70°C and exposed to a UV light having a wave length between 200 and 300 nm for 6 minutes.

10 Then, sterilisation of the coated catheter was carried out while wetted with a solution of PVP using irradiation.

The catheter were lubricious in wet condition and had a high abrasion resistance.

Example 1

Determination of the water retention time in minutes and the friction force in N

15 when using the aqueous wetting liquid according to the invention as compared to the use of saline for wetting the coating.

A cross-linked coating prepared according to Example a, and the following commercial catheters: an EasiCath® catheter, from Coloplast A/S, a LoFric® catheter from Astra AB, a PuriCath® catheter from Maersk Medical, an

20 AquaCath® catheter from EMS, and a Uro-flo Silky catheter from Simcare were tested for determination of the water retention time and the friction. The coated catheters were compared to an uncoated raw catheter having no hydrophilic coating.

All catheters were stored in a 6% solution of PVP Plasdone K-25 or in saline and

25 sterilised by irradiation, and water reretention of the coatings and the force of friction were determined as described above.

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The results are summarised in the below Table 1:

Table 1.

Liquid	0.9 % saline	6% Plasdone K-25	0.5% CMC	0.15% Xantha ne	0.9% Saline	6% Plasdone K-25
Coating	Water retention (minutes)				Friction Force (N)	
Example a	1 - 3	9	9	9	0.06	0.04
EasiCath®	1 - 2	7			0.1	0.04
LoFric®	1 - 2	5 - 7			0.05	0.02
PuriCath®	1 - 2	5			0.32	0.25
AquaCath®	1 - 2	3			0.08	0.06
Uro-flo Silky	1 - 2	1 - 2			0.7	0.35
Raw catheter	0	0			0.8	0.8

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Claims

1. A method for sterilising a medical device comprising a hydrophilic coating using radiation said method comprising the steps bringing the medical device having such coating in contact with an aqueous liquid for wetting the hydrophilic
5 coating , said liquid comprising a solution of a hydrophilic polymer and sterilising the device by applying a sufficient amount of radiation.
2. A method as claimed in claim 1, characterised in that the hydrophilic polymer is a synthetic polymer.
3. A method as claimed in claim 2, characterised in that the hydrophilic polymer
10 is selected from the group consisting of polyvinylpyrrolidone or copolymers containing N-vinylpyrrolidone, poly(meth)acrylic acid or copolymers containing (meth)acrylic acid or (meth)acrylic acid esters, polyacrylamides, polyvinylalcohol and copolymers of partially saponified vinylacetate copolymers, polyethylenglycol, polyvinylmethylether, polyvinylmethylether-maleic anhydride
15 and copolymers containing maleic-anhydride or maleic-acidesters or copolymers containing vinylmethyl-ether.
4. A method as claimed in claim 3, characterised in that the hydrophilic polymer is polyvinylpyrrolidone or a copolymer thereof.
5. A method as claimed in claim 1, characterised in that the hydrophilic polymer
20 is a polysaccharide.
6. A method as claimed in claim 5, characterised in that the hydrophilic polymer is selected from the group consisting of water soluble polysaccharides such as carboxymethylcellulose (CMC) or hydroxyethylcellulose and Xanthane or a derivative thereof.
- 25 7. A method as claimed in claim 6, characterised in that the hydrophilic polymer is CMC or a derivative thereof.

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8. A sterilised set comprising a medical device provided with a hydrophilic coating and an aqueous liquid for wetting the hydrophilic coating wherein said device is in contact with the aqueous liquid, wherein said set has been sterilised using radiation while in contact with said liquid comprising a solution of a hydrophilic polymer.
9. A set as claimed in claim 8 wherein the aqueous liquid is placed in the package also comprising the medical device provided with a hydrophilic coating.
10. A method of protecting the hydrophilic coating of a medical device having such coating during sterilising using radiation, characterised in that the coating is brought into contact with an aqueous solution comprising a hydrophilic polymer and exposed for the radiation while in contact with the aqueous solution.
11. A medical device comprising a hydrophilic coating said medical device showing, after sterilisation using radiation, a water drain off time > 3 minutes and a friction force of < 0.05 N when testing a 10 cm tube having the hydrophilic coating fixed on a stainless steel plate with two stainless steel rods as shown in ASTM 1894-93.
- 12 A method of preparing a sterilised catheter having a crosslinked two-layer hydrophilic coating comprising the steps of
- a) preparing a solution of polyvinyl pyrrolidone dissolved in an ethanol/gamma butyrolactone solvent mixture,
 - b) dipping a raw catheter in the solution and letting it dry at ambient temperature,
 - c) dipping the resulting catheter in a PVP-solution containing urea and an ethanol/gamma butyrolactone (85/15) solvent mixture,
 - d) further drying at elevated temperature,
 - e) cross-linking the polyvinylpyrrolidone by exposing the coated catheter to UV-light having a wave length range between 200 and 300 nm. for from ½ to 15 minutes, and
 - f) sterilising the coated catheter while wetted with a. solution of PVP by irradiation

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13. A method of preparing a sterilised catheter having a crosslinked hydrophilic coating with unsaturated Poly(methyl vinyl ether/maleic anhydride)/hydroxyethyl-methacrylate(HEMA) prepolymers comprising the steps of

- a) preparing a solution of poly(methyl vinyl ether/maleic anhydride) in acetone in
5 a reaction vessel equipped with a stirrer, keeping the reaction mixture at room temperature while adding 1-methylimidazole as a catalyst and hydroxyethyl-methacrylate dropwise to the stirred polymer solution during a period of 30 minutes,
- b) stirring the mixture for from few minutes to 10 hours at room temperature,
- 10 c) preparing a primer mixture by dissolving a medical grade polyurethane and the poly(methyl vinyl ether/maleic anhydride)/HEMA unsaturated prepolymer in a mixture of THF and acetone,
- d) coating a raw catheter with a primer by dipping in the resulting solution in a manner known per se,
- 15 e) dipping the resulting catheter in the solution of poly(methyl vinyl ether/maleic anhydride)/HEMA unsaturated prepolymer in acetone for applying a top coat,
- f) drying the resulting catheter,
- g) cross-linking the poly(methyl vinyl ether/maleic anhydride)/HEMA unsaturated prepolymerpolyvinylpyrrolidone by exposing the coated catheter to 5 M
20 rads from a high energy electron beam source, and
- h) sterilising the coated catheter while wetted with a solution of PVP by irradiation.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 99/00641

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61L 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9819729 A1 (COLOPLAST A/S), 14 May 1998 (14.05.98) --	1-13
A	WO 9623602 A1 (SCHNEIDER (USA) INC.), 8 August 1996 (08.08.96), page 39, line 1 - line 11; page 64, line 14 - line 18 --	1-13
A	EP 0217771 A1 (ASTRA MEDITEC AB), 8 April 1987 (08.04.87) --	1-13
A	WO 9506670 A1 (NEPERA, INC.), 9 March 1995 (09.03.95) --	1-13

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

2 March 2000

Date of mailing of the international search report

19.04.00

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INTERNATIONAL SEARCH REPORT

International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

02/12/99

International application No.

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